II. REMARKS/ARGUMENTS

A. Status of Claims

Claims 38, 47, 49-56, and 58-66 were amended without prejudice or admission.

New claims 69 to 76 were added.

Applicants submit that support for the amended and new claims can be found as follows.

Support for "a therapeutically effective amount of a COX-2 inhibitor together with a dose of an opioid analgesic" in claim 38 can be found, e.g., on page 9, lines 13-15, of the specification and page 15, lines 14-23, of U.S. application Serial No. 60/059,195 ("the provisional application") ("[t]he present invention encompasses a method of inhibiting COX-2 and treating COX-2 mediated diseases comprising administering to a patient in need of such treatment a non-toxic therapeutically effective amount of the COX-2 inhibitor and opioid analgesic combination of the present invention ...").

Support for the COX-2 being nimesulide and the opioid analgesic being oxycodone in claims 38, 54 and 63 can be found, e.g., on page 19, lines 15-20, of the original specification and page 12, lines 11-16, of the provisional application ("[p]referred combinations of the invention comprise an effective amount of a COX-2 inhibitor selected from the group consisting of nimesulide ... and an effective amount of an opioid analgesic selected from the group consisting of ... oxycodone ...").

Support for the oxycodone ratio of "10:1" in claims 47, 64 and 74 can be found, e.g., on page 20, line 22, of the original specification and page 13, line 17, of the provisional application ("oxycodone 40 mg plus 4 mg of nimesulide").

Support for "the COX-2 inhibitor is combined with carrier materials to produce a single dosage form having the COX-2 inhibitor and the opioid analgesic" in claim 49 and for "sustained

release carrier" in claims 50, 65 and 66 can be found, e.g., on page 18, lines 21-24, of the original specification ("[t]he amount of COX-2 inhibitor that may be combined with the carrier materials to produce a single dosage form having COX-2 inhibitor and opioid analgesic ..."), page 11, lines 4-6, of the original specification and page 7, line 21, to page 8, line 5, of the provisional application ("... the oral solid dosage form include a sustained release carrier which causes the sustained release of the opioid analgesic, or both the opioid analgesic and the COX-2 inhibitor ...").

Support for "an oral dosage form consisting of (i) a COX-2 inhibitor in an immediate release form; (ii) an opioid analgesic in a sustained release form; and (iii) and at least one pharmaceutically acceptable excipient" in claim 54 can be found, e.g., on page 24, line 31, to page 25, line 1, of the original specification and page 19, lines 8-9, of the provisional application specification ("[t]he sustained release dosage form may include the opioid analgesic in sustained release form and COX-2 inhibitor ... in immediate release form ...").

Support for administration "2 times per day" in claim 55, can be found, e.g., on page 20, lines 29-32, of the original specification, and page 13, lines 23-26 ("[a] composition comprising any of the above-identified combinations of opioid analgesics and COX-2 inhibitors may be administered in divided doses ranging from 2 to 6 times per day ...").

Support for "COX-2 inhibitor in an immediate release form ... coated onto a tablet comprising the opioid analgesic in the sustained release form" in claim 60 can be found, e.g., on page 24, line 31, to page 22, line 8, of the original specification, and page 8, lines 16-17 ("... the tablet contains the opioid analgesic within a sustained release matrix and COX-2 inhibitor coated into the tablet into as an immediate release layer.").

Support for "once-daily" administration in claims 62, 76 and 76 can be found, e.g., on page 22, line 29-30, of the original specification and page 16, lines 14-16, of the provisional application ("[t]he combination of COX-2 inhibitor and oral opioid analgesics may be

formulated to provide for an increased duration of analgesic action allowing once-daily dosing ...").

Support for "a combination of a COX-2 inhibitor and an opioid analgesic in an admixture of excipients" in claim 63 can be found, e.g., on page 23, lines 4-30, of the original specification and page 16, line19, to page 17, line 5, of the provisional application ("[t]he combination of COX-2 inhibitor and an opioid analgesic can be employed in admixtures with conventional excipients ...").

Support for "pain without inflammation" in claims 63, 71 and 73 can be found, e.g., on page 21, line 29, of the present specification and page 15, lines 7-8, of the provisional application ("[c]ompositions of the invention present the opportunity for obtaining relief from moderate to severe pain ... without inflammation").

Support for new claim 69 can be found, e.g., on page 18, lines 21-24, of the original specification ("[t]he amount of COX-2 inhibitor that may be combined with the carrier materials to produce a single dosage form having COX-2 inhibitor and opioid analgesic ...") and on page 23, lines 4-30, of the original specification and page 16, line19, to page 17, line 5, of the provisional application ("[t]he combination of COX-2 inhibitor and an opioid analgesic can be employed in admixtures with conventional excipients ...").

Support for "4 mg of nimesulide" in claims 70 and 75, can be found, e.g., on page 20, line 20, of the original specification, and page 13, line 17, of the provisional application ("4 mg").

Applicants respectfully submit that no new matter was added by virtue of the present amendments and that claims 38 and 47-76 will be pending once the present amendment is entered.

Applicants submit that claims 38 and 47-76 read on the species elected in the response filed on June 23, 2008.

B. Priority

In the Office Action, the Examiner asserted that certain features of the examined claims are not supported by the parent application, U.S. application No. 09/154,354, filed September 17, 1998, and U.S. application No. 60/059,195, filed on September 17, 1997, which are relied upon for an earlier effective filing date ("the earlier applications").

Applicants respectfully disagree with the Examiner's assertion and submit that the examined claims are disclosed in the earlier applications, and are entitled to the September 17, 1997 priority date.

In an effort to advance prosecution, the claims were amended, e.g., to resemble the language of the earlier applications. Support for the amended claims can be found as described in the Status of the Claim section above.

Applicants respectfully request that the September 17, 1997 priority date be acknowledged.

C. Rejection- 35 U.S.C. § 103

Claims 38, 47-53 and 54-68 were rejected under 35 U.S.C. § 103(a) over U.S. Patent No. 4,569,937 to Baker et al. in view of Swingle et al. (Drugs Exptl. Clin. Res. Vol. X (8-9)(1984) pages 587-597) and/or Rabasseda (Drugs of Today Vol. 32, No. 5 (1996) pages 365-384) and further in view of U.S. Patent No. 5,472,712 to Oshlack et al. or U.S. Patent No. 6,294,195 to Oshlack et al..

The rejection is respectfully traversed, for the reasons set forth in the response filed on November 5, 2008, hereby incorporated by reference.

Independent claims 38, 54 and 63 are directed to a method of treating pain by administering nimesulide in combination with oxycodone as recited in these claims.

Applicants respectfully submit that the cited references (alone or in combination) do not teach or suggest that nimesulide may be administered together with an additional analgesic agent (i.e., oxycodone), e.g., because the Rabasseda and the Swingle references (which are relied upon for the disclosure of nimesulide) describe administration of nimesulide by itself, without any additional active agents.

In response to the Examiner's statement on page 12 of the Office Action that "evidence provided by Beaver (1984 Combination Analgesics. The American Journal of Medicine pp 38-53) and Beaver II (1992 Evaluation and Treatment of Chronic Pain Ch 29 Nonsteroidal anti-inflammatory analgesics and their combination with opioids) indicates the idea of combining NSAIDs with opioids was well established in the art at the time of the presently claimed invention was made," Applicants note that the 1984 Beaver Article states on page 38, e.g., that "**[u]nless** there is sufficient evidence that use of an analgesic combination is likely to yield therapeutic results unobtainable with a suitable dose of one of its constituents, **a single analgesic alone should be used**." (emphasis added). Applicants further note that the 1992 Beaver article states on page 378, e.g., that "**[i]f** an optimal regimen of an NSAID alone does not provide adequate analgesia, one can add a weak opioid to the existing NSAID regimen."

Applicants submit that there is nothing in the cited references that indicates that administration of nimesulide alone will not provide adequate analgesia. Therefore, Applicants respectfully submit that, in accordance with the guidance provided by the Beaver articles, a skilled person would not have been motivated by the cited references to administer nimesulide together with an additional analgesic agent (i.e., oxycodone).

Accordingly, Applicants submit that independent claims 38, 54 and 63 and their dependent claims are not rendered obvious by the combination of the cited references.

With further regard to independent claim 54, Applicants respectfully submit that the combination of the cited references does not teach "an oral dosage form consisting of (i) a COX-2 inhibitor in **an immediate release form**; (ii) an opioid analgesic in a sustained release form; and (iii) and at least one pharmaceutically acceptable excipient" as recited in claim 54 (emphasis added). In response to the Examiner's statement on page 6 of the Office Action that "'195 teaches [that] a second drug may either be incorporated with an opioid in a controlled release matrix ... or may be part of a controlled release coating ...," Applicants respectfully submit that a second drug incorporated into a controlled release matrix or a controlled release coating does not read on a drug "in an immediate release form" as recited in claim 54. Accordingly, Applicants submit that claim 54 and its dependent claims are not rendered obvious by the combination of the cited references for these additional reasons.

With further regard to claims 47 and 64, Applicants respectfully submit that the combination of the cited references does not teach or suggest administration of oxycodone to nimesulide "in a ratio of 10:1" as recited in these claims. Applicants note that the ratio of 10:1 means that the administered amount of the oxycodone is 10 times higher than the administered amount of nimesulide in the methods of claims 47, 64 and 74. The Baker patent on the other hand states that the weight ratio of a narcotic analgesic to ibuprofen in its compositions "is from about 1:1 to about 1:800." *See Baker patent, column 2, lines 11-16.* In other words, the administered amount of the narcotic analgesic in the Baker patent is either equal or lower than the amount of ibuprofen in Bakers' compositions. Accordingly, Applicants submit that the Baker patent does not teach or suggest administration of oxycodone to nimesulide "in a ratio of 10:1." Accordingly, claims 47 and 64 are not rendered obvious by the combination of the cited references for this additional reason.

In response to the Examiner's reliance on *In re Aller*, Applicants respectfully note that the claims at issue in *In re Aller* did were not directed to a method of treating pain, and, therefore, the Examiner's reliance on *In re Aller* may be inappropriate.

With further regard to claim 62, Applicants submit that the combination of the cited references does not teach or suggest administration of nimesulide **once-daily** as recited in claim 62. Applicants respectfully note that the Rabasseda reference describes twice daily administration of nimesulide (Abstract and page 373, right column), and the Swingle reference describes four times daily administration of nimesulide (page 592) rather than once-daily administration. Accordingly, Applicants submit that the cited references do not teach or suggest once-daily administration of nimesulide as recited in claim 62. Claim 62 is not rendered obvious by the cited references for this additional reason.

For the foregoing reasons, withdrawal of the rejection is respectfully requested.

D. Rejection- 35 U.S.C. § 112

Claims 38 and 47-68 were rejected under 35 U.S.C. § 112, first paragraph.

The rejection is respectfully traversed.

Claims 38 and 47-68 are directed to methods of treating pain by administering a COX-2 inhibitor (i.e., nimesulide) in combination with an opioid analgesic (i.e. oxycodone).

Applicants respectfully submit that claims 38 and 47-68 are fully supported by the original specification. For example, the original specification states that the invention relates, e.g., "to the use of a pharmaceutical combination of a COX-2 inhibitor together with an opioid analgesic to provide effective pain management in humans." See page 9, lines 28-30 of the original specification. The original specification further states that "[p]referred combinations of the invention comprise an effective amount of a COX-2 inhibitor selected from the group

consisting of nimesulide ... and an effective amount of an opioid analgesic selected from the group consisting of ... oxycodone ...." See page 19, lines 15-20, of the original specification. The original specification also describes a dosage form comprising oxycodone and nimesulide. See, e.g., page 20, lines 22-23, of the original specification.

Accordingly, Applicants respectfully submit that the original specification makes it clear that Applicants were in possession of methods of treating pain by administering a COX-2 inhibitor (i.e., nimesulide) in combination with an opioid (i.e. oxycodone) and a dosage form comprising a COX-2 inhibitor (i.e., nimesulide) and an opioid (i.e., oxycodone).

In response to the Examiner's regarding claim 56, Applicants respectfully submit that additional support for claim 56 can be found, e.g., on page 24, lines 28-30, of the original specification ("[t]he sustained release dosage form may optionally include a sustained release carrier which is incorporated into a matrix along with the opioid, or which is applied as a sustained release coating").

In response to the Examiner's comments regarding claims 57, 67 and 68, Applicants respectfully submit that these claims are supported, e.g., on page 22, lines 5-22, of the original specification, which recites:

> The present invention encompasses a method of inhibiting COX-2 and treating COX-2 mediated diseases comprising **administering to a patient in need of such treatment a non-toxic therapeutically effective amount of the COX-2 inhibitor and opioid analgesic combination of the present invention.** These diseases include moderate to severe pain arising from many different etiologies, including but not limited to cancer pain and post-surgical pain, fever and inflammation of a variety of conditions including rheumatic fever, symptoms associated with influenza or other viral infections, common cold, low back and neck pain, dysmenorrhea, headache, toothache, sprains and strains, myositis, neuralgia, synovitis, arthritis, including rheumatoid arthritis, degenerative joint diseases (osteoarthritis), gout and ankylosing spondylitis, bursitis, burns, and injuries. Further, the combination of COX-2 inhibitor and opioid analgesic is useful as an alternative to conventional non-steroidal anti-inflammatory drugs or combinations of NSAID'S with other drugs particularly where such non-steroidal anti-inflammatory drugs may be

> contra-indicated such as in patients with peptic ulcers, gastritis, regional enteritis, ulcerative colitis, diverticulitis or with a recurrent history of gastrointestinal lesions; GI bleeding, coagulation disorders including anemia such as hypoprothrombinemia, haemophilia or other bleeding problems; kidney disease; those prior to surgery or taking anticoagulants.

Specification, page 22, lines 5-22 (emphasis added).

As stated above, analgesic combinations of the present invention include a combination of oxycodone and nimesulide. See page 19, lines 15-20, of the original specification. Accordingly, Applicants submit that claims 57, 67 and 68 are supported by the specification.

In response to the Examiner's comments regarding claims 58 and 59, Applicants submit that these claims are supported, e.g., on page 25, lines 9-17. ("[a]n oral dosage form according to the invention may be provided as, for examples ... particles ...[which] have diameter from about 0.1 mm to about 2.5 mm").

For the foregoing reasons, Applicants submit that claims 8 and 47-68 are supported by the specification and request withdrawal of the rejection.

Withdrawal of the rejection is respectfully requested.

III. CONCLUSION

An early and favorable action on the merits is earnestly solicited. The Examiner is respectfully requested to contact the undersigned at the telephone number provided below in the event that a telephonic interview will advance the prosecution of the application.

Respectfully submitted,
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